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The safety of anti PD-1 therapeutics for the treatment of melanoma

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	Pembrolizumab (2mg/kg every 3w)		Pembrolizumab (10mg/kg every 3w)		Nivolumab (3mg/kg every 2w)	
	All AEs	**Grade 3-4 AEs**	**All AEs**	**Grade 3-4 AEs**	**All AEs**	**Grade 3-4 AEs**
Phase I	82%[61]	15%[61]	82% [61]	8%[76]	68% [18]	16% [18]
Phase II	68%[62]	11%[62]	74% [62]	14%[62]		
Phase III			72.9%[20]	10.1%[13] (G 3-5)	82.1% [22]	43.5% [22]

vere or 3 AE	Pembrolizumab (2mg/kg every 3w)[61-63, 69]	Pembrolizumab (10mg/kg every 3w)[61-63]	Nivolumab (3mg/kg every 2w)[18, 22]
a	1%	1%	>1%
s	1%	-	1%
nitis	1%	1%	0.3%
on	1%	-	-
e in te ansferase	-	0.4%	1%
	1%	-	-
e in e	1%	-	-
ysitis	1%	0.4%	0.3%
		0.4-1%	0.3%
	-	-	0.3%
titis	-	1%	
ral motor thy	1%	-	-
alopathy	1%	-	-
oskeletal ss or pain	1%	1%	-

	Established management	Proposed management	
		Published in literature[97-99]	By authors
	Systemic steroids 1-2 mg/kg/d + consider prophylactic antibiotics, if no improvement within 72-120h -> Add infliximab 5 mg/kg (if perforation ruled out)	Systemic steroids 0.5-2 mg/kg/d + consider prophylactic antibiotics; if no improvement after 48-72h -> Infliximab 5mg/kg (if perforation ruled out); if no improvement -> tacrolimus/MMF 500-1000 mg/d	Infliximab 5 mg/kg single infusion, if no improvement or recurrence – 2nd infusion
n	G3 – hold treatment until resolves to grade 0-1, discontinue if not resolved within 12 weeks G4 – permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
	Systemic steroids 1-2 mg/kg/d + prophylactic antibiotics; if no improvement within 72-120h-> Add MMF 1000 mg b.d.	Systemic steroids 1-2 mg/kg/d; if no improvement -> MMF 500-1000 mg/d b.d.	MMF 500-1000 mg/d b.d. until 6 weeks of normalization
n	Permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
		Systemic steroids 10 – 20 mg/d, if no improvement -> systemic steroids 1 mg/kg/d	MTX 15-30 mg/weekly, if no improvement -> Infliximab 5 mg/kg
n	G3 – hold treatment until resolves to grade 0-1, discontinue if not resolved within 12 weeks G4 – permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
is	Systemic steroids 2-4 mg/kg/d +/- empiric antibiotics; if no improvement within 48h-> Add additional immunosuppression	Systemic steroids 1-4 mg/kg/d +/- empiric antibiotics; if no improvement -> additionally infliximab 500 mg/kg/d / MMF 500-1000 mg/d b.d.	Infliximab 5 mg/kg + Mycofenolat mofetil 500-1000 mg/d b.d.
n	Permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
	Systemic steroids 1-2 mg/kg/d	Topical steroids; if no improvement -> Systemic steroids 0.5-1 mg/kg/d	Topical steroids (class IV) for 2 weeks, then switch to topical calcineurin inhibitors
n	G3 – hold treatment until resolves to grade 0-1, discontinue if not resolved within 12 weeks G4 – permanently discontinue	Hold treatment until resolves to G 0-1, reintroduce if stable G 0-1 for 6 weeks	
	If symptomatic: systemic steroids 1-2 mg/kg/d + hormone replacement therapy	Symptomatic hyperthyroidism: systemic steroids 1-2 mg/kg/d + consider methimazole Symptomatic hypothyroidism + abnormal laboratory results + hormone replacement	Symptomatic hyperthyroidism: betablockers (if tachycardia), methimazole only if anti-TPO antibodies are detected Symptomatic hypothyroidism + abnormal laboratory results + hormone replacement

Article highlights

- Therapy with anti-PD-1 antibodies is a relatively novel treatment option now recomended as first line therapy for metastasized melanoma, independet of *BRAF* mutation
- Anti-PD-1 antibodies prevent PD-1 from binding to PD-L1 and following downregulation of T-cells
- Approved anti-PD-1 antibodies, pembrolizumab and nivolumab, show good response rates and tolerability
- Majority of adverse events associated with anti-PD-1 therapy are likely immune related
- They are usually mild in severity and can be managed with immunomodulatory medications and treatment interruption